MANAGING STATIN-RELATED MYOPATHY

Statins are lipid-lowering agents that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting step in cholesterol production. A notable adverse effect associated with statins is muscle pain; statin-related myopathy includes myalgia, myositis, and rhabdomyolysis. Minimizing the risk of myopathy is important to improve patient adherence and tolerance. This issue of CLIPS briefly summarizes an article that reviews the incidence, pathophysiology, and risk factors for statin-induced myopathy as well as possible treatment strategies. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Myopathy Background

- Definitions of myopathy terms vary depending on the source. The following definitions are from the American College of Cardiology (ACC), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI).
  - Myalgia: muscle pain or weakness without an elevation in creatine kinase levels.
  - Myositis: muscle pain or weakness with an elevation in creatine kinase levels.
  - Rhabdomyolysis: a life-threatening condition that presents with muscle pain or weakness, a significant elevation in creatine kinase levels ( > 10 x upper limit of normal), and an elevation in creatinine (often presents with brown urine and urinary myoglobin).
- The cause of statin-related myopathy remains uncertain. Some possible explanations include: decreased cholesterol synthesis in skeletal muscle cells resulting in membrane instability, depletion of coenzyme Q10, depletion of isoprenoids, and mitochondrial dysfunction. However, each of these theories has limitations.
- The frequency of myopathy ranges from 1% to 10% depending on the source of information (i.e., clinical trial, observation trial, or the Food and Drug Administration Adverse Event Reporting System [AERS]).
- The most frequently reported condition is myalgia with reports of rhabdomyolysis being extremely rare.
- Certain statins may have an increased frequency of muscle symptoms. For example, based upon the results from a single observational study, the rate of symptoms was 5.1% for fluvastatin (Lescol®), 10.9% for pravastatin (Pravachol®), 14.9% for atorvastatin (Lipitor®), and 18.2% for simvastatin (Zocor®). According to AERS, the rates of muscle events with rosuvastatin (Crestor®) are proportionately the same or lower than other statins.

Clinical Features and Monitoring

- Based on various types of studies, the onset of statin-related myopathy ranges from 1 to 12 months after beginning therapy.
- The major sites of myopathy according to an observational study were the thighs or calves, although the pain may be generalized or associated with tendons.
- Patients may express muscle symptoms as heaviness, stiffness, cramping, or exertional weakness.
- The duration of muscle pain varies between patients and may be sporadic.
- Practitioners should evaluate muscle symptoms throughout therapy and draw serum creatine kinase levels if symptoms develop. Routine serum creatine kinase levels are not recommended in asymptomatic patients.

Risk Factors for Statin-Related Myopathy

- Risk factors for statin-related myopathy are divided into patient-related factors and treatment-related factors.
- Patient-related risk factors include: alcoholism, increased age, female gender, small body frame, hypothyroidism, intense physical activity, multiple medications, additional medical conditions (e.g., renal or hepatic disease), recent major surgery, significant grapefruit juice consumption, or unexplained cramps.
Risk Factors for Statin-Related Myopathy (continued)
- Patients with a history of myopathy associated with lipid-lowering agents, a history of creatine kinase elevations, or a family history of myopathy with or without lipid-lowering therapy are also at increased risk.
- Treatment-related factors include: high statin dosages and drug-drug interactions.
  - Simvastatin, lovastatin, and atorvastatin undergo CYP3A4 metabolism and interact with CYP3A4 inhibitors.
  - Examples of CYP3A4 inhibitors are protease inhibitors, cyclosporine, amiodarone, verapamil, antifungals, macrolide antibiotics, and nefazadone.
  - Fluvastatin and rosuvastatin are primarily metabolized by CYP2C9; pravastatin undergoes renal metabolism.
- Concomitant use of fibrates with statins (especially gemfibrozil [Lopid®]) also increases the risk of myopathy.
- According to one observational study, statin duration of greater than 3 months may reduce the risk of statin-related myopathy.

Management of Statin-Related Myopathy
- Two guidelines have been published to manage statin-related myopathy (by the ACC/AHA/NHLBI and National Lipid Association). These guidelines vary in their recommendations. The information and table below present a common method for managing myopathy related to symptoms and creatine kinase levels.
- Before initiating statin therapy, obtain a baseline assessment of myopathy symptoms (pain level, location, and type) and serum creatine kinase to help differentiate the cause of myopathy occurring during therapy.
- Practitioners should always assess for other causes of creatine kinase elevation and myopathy. Other conditions may present similarly to statin-induced myopathy, with hypothyroidism being a significant example.
- Discontinuation of statin therapy during the perioperative period of a major surgery is recommended.
- The following table displays recommendations for managing myopathy during statin therapy.

<table>
<thead>
<tr>
<th>Serum Creatine Kinase Level</th>
<th>Symptomatic</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 × upper limit of normal</td>
<td>No</td>
<td>Continue to titrate statin to achieve the LDL goal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor for symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Draw creatine kinase levels every 3 to 6 months</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>Discontinue therapy or decrease dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor until resolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After resolution, may initiate a different statin</td>
</tr>
<tr>
<td>&gt; 5 × upper limit of normal</td>
<td>No</td>
<td>Discontinue therapy or decrease dose</td>
</tr>
<tr>
<td></td>
<td></td>
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Alternative Therapeutic Options
- Alternative therapeutic options include: changing to a different statin, utilizing nondaily statin dosing, and adding / switching to ezetimibe [Zetia®] with or without a bile acid-binding resin.
- Fluvastatin and rosuvastatin are options if patients have myopathy with other statins.
- Fluvastatin appears to have the lowest rates of myopathy. A controlled clinical trial of patients with previous statin-related myopathy demonstrated repeated muscle pain occurring in only 17% of patients taking fluvastatin 80 mg and 14% of patients taking fluvastatin 80 mg plus ezetimibe 10 mg. Also according to AERS, there are currently no reports of rhabdomyolysis with fluvastatin.
- Rosuvastatin has a theoretical benefit in patients taking multiple medications due to CYP2C9 metabolism (i.e., low potential for metabolism-related interactions) and the high potency of this statin.
- Alternate-day atorvastatin may provide LDL lowering similar to daily atorvastatin dosing although testing is needed in statin-intolerant patients.
- Nondaily rosvuavstatin dosing (alternate-day or once-weekly) is effective in previously statin-intolerant patients.
- Ezetimibe with or without the use of bile acid-binding resins (e.g., coleselam [Welchole®]) may be prescribed to lower LDL levels in patients intolerant of statin therapy. However, data documenting a reduced rate of cardiovascular disease with ezetimibe are lacking.
- Coenzyme Q10 supplementation is generally not recommended due to the lack of beneficial evidence. However, supplementation may be useful in patients who do not respond to other strategies.
- For mixed dyslipidemias, fenofibrate (Tricor®) is preferable to gemfibrozil and should be prescribed cautiously.

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